

## ORIGINAL ARTICLE

## FETAL INFECTIONS OPTIMIZATION OF PREGNANCY AND DELIVERY INTRODUCTION

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### ABSTRACT

**The aim:** Improving perinatal outcomes in pregnant women at high risk of intrauterine infection by developing diagnostic criteria and algorithms for managing pregnancy and childbirth.

**Materials and methods:** The study of pregnancy and childbirth was conducted in 72 patients at high risk of IUI, which formed the main group. The control group consisted of 64 patients with a low infectious risk of IUI. Culture, bacterioscopic and biochemical methods were used to identify microorganisms. Peculiarities of infection in the examined women were investigated by determining the concentration of Ig M and IgG in the blood serum and performed polymerase chain reaction for measles virus, cytomegalovirus, parvovirus B19. Serum for the presence of specific immune globulins to these pathogens was examined by ELISA. Comprehensive ultrasound examination in B-mode was performed to determine the fetometry of the fetus and assess its development with the determination of the estimated mass, location, size and structure of the placenta, the amount of amniotic fluid. To determine the condition of the fetus, a Doppler study of blood flow in the uterine arteries, umbilical artery, middle cerebral artery of the fetus and venous duct.

**Results:** Analyzing the course of this pregnancy in women of the studied groups threatened miscarriage and the threat of premature birth occurred in 24 (33.3%) cases, with signs of isthmic-cervical insufficiency were diagnosed in 13 (18.1%) patients. In the control group of patients, the threat of abortion was diagnosed in 15 (23.4%) patients. According to ultrasound examination, patients in the main group in 12 (16.7%) cases were diagnosed with fetal growth retardation, in 25 (34.7%) patients at high risk of IUI there were changes in the placenta, namely, hyper echogenic inclusions in the placenta occurred in 7 (9.7%) cases, dilation of the intervillous space in 8 (11.1%) cases, placental hyperplasia in 7 (9.7%) cases, polyhydramnios was diagnosed in only 5 (6, 9%) cases, with 1 (1.4%) acute polyhydramnios in patients with signs of acute respiratory viral infection during pregnancy.

**Conclusions:** Women at high risk for IUI require close monitoring of the fetus due to the increased frequency of hemodynamic changes in uteroplacental-fetal circulation, including fetal-placental – 22.2% and the occurrence of intrauterine growth retardation.

Women with suspected cytomegalovirus infection require determination of seroconversion; in case of immunologically confirmed infection, it is desirable to recognize PCR for cytomegalovirus in the amniotic fluid in order to determine further management and monitoring of this pregnancy.

**KEY WORDS:** fetal growth retardation, antibiotic prophylaxis, miscarriage, inflammatory diseases, cytomegalovirus infection

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### INTRODUCTION

Recently, more and more attention has been paid to increasing the frequency of intrauterine infection (IUI) in developing the perinatal pathology, in particular in the emergence of fetus critical condition [1,5,9,16]. In most countries, the registered increase in the role of IUI in forming the pathology of the perinatal period and the situation with IUI is equated to an epidemic. One of the most urgent tasks of perinatology at present is the problem of predicting fetal IUI using methods available in modern obstetrics. Despite the fact that many works are devoted to this problem, so far there is no holistic view of the course of pregnancy, fetal development and the likelihood of its intrauterine infection when infecting the mother. There are no common views on the pathogenesis, prevention, treatment of intrauterine infections, obstetric tactics in IUI [2, 3, 8, 17, 20].

A typical fetal response to infection is developing the fetal inflammatory response syndrome, which is difficult to verify in the fetus and can only be determined postnatally by immunological studies in the newborn (determination of cytokines and chemokines such as interleukins, C-reactive protein and matrix metalloproteinase) [4, 6, 9, 11]. The cytomegalovirus infection (CMV) is known to be the most common cause of neurosensory hearing loss and mental retardation 0.2 – 2.2% of all newborns, 10-15% of congenitally infected children will have symptoms at birth: fetal growth retardation, microcephaly, hepatosplenomegaly, petechiae, jaundice of newborns, chorioretinitis, thrombocytopenia and anemia. Most congenitally infected children (85-90%) do not have any signs of the disease after birth, but 5% – 15% of them will later develop complications such as neurosensory deafness, psychomotor developmental

delay and visual impairment [6, 13, 17, 19]. Parvovirus-B19 infection is a common cause of fetal anemia in the second trimester of pregnancy. This necessitates intrauterine replacement blood transfusion [14, 15, and 17]. The risk of developing fetal chickenpox syndrome is 1-2% with infection during pregnancy up to 20 weeks and is manifested by neurological disorders (mental retardation, microcephaly, hydrocephalus, convulsions, Horner's syndrome), ocular abnormalities, optic nerve atrophy, microphthalmia, cataract, nystagmus), abnormalities in the development of the extremities (atrophy, paresis, hypoplasia), gastrointestinal disorders (gastro esophageal reflux, intestinal atresia or stenosis) [1, 7, 10]. Group B *Streptococcus*, or *Streptococcus agalactiae*, are gram-positive bacteria that cause infectious disease primarily in newborns, but also in pregnant women, postpartum women (uterine sub involution and early acute pyelonephritis). Early onset of the disease in newborns (during the first week of life): respiratory distress, apnea, or other signs of sepsis during the first 24-48 hours of life. The most common clinical syndrome of the disease with an early onset is sepsis and pneumonia, rarely meningitis. There is mortality of the disease with early onset up to 50% without treatment; during therapy – 4 - 6%. Mortality is higher among premature infants, at about 20%. Infection of the fetus occurs intranatally in pregnant women who are carriers of group B *streptococcus* [14, 16, and 19].

The mechanism of developing the intrauterine infection is quite complex and many aspects of this problem are still debatable, need further study [20, 21, 22]. A significant part of diseases in pregnant women, which lead to intrauterine infection of the fetus, occurs in subclinical or latent, asymptomatic form, have no characteristic clinical manifestations, which significantly complicates the diagnosis of this pathology in the antenatal period [2, 3, 7, 23].

So, contradictory data on the informativeness and diagnostic value of various methods for predicting the occurrence of IUI, as the reasons for developing the critical state of the fetus and newborn, indicate the need to systematize the data and conduct a comparative analysis. Searching and developing the algorithm of diagnostics, forecasting the emergence of IUI and its prevention by methods available in practical obstetrics, estimating the informativeness of the received results is an actual task of modern perinatology [7, 9, and 12].

## THE AIM

Improving perinatal outcomes in pregnant women at high risk of intrauterine infection by developing diagnostic criteria and algorithms for managing pregnancy and childbirth.

## MATERIALS AND METHODS

To achieve this goal, a comprehensive study of pregnancy and childbirth was conducted in 72 patients at high risk of IUI, who were registered and treated in the city clinical maternity hospital №2 in Kyiv, which formed the main group. Criteria for inclusion of patients in the study were:

the presence of a children's birth history or fetuses with signs of intrauterine infection, confirmed clinically and/or morphologically. The control group consisted of 64 patients with a low infectious risk of IUI.

Clinical examination of patients was performed on a specially designed questionnaire, which included primarily a detailed collection of anamnestic data to identify possible risk factors for IUI. The analysis of pregnancy consisted of collecting data on the course of gestation, data of additional instrumental and laboratory methods of research, in particular data of bacterioscopic, bacteriological study of material from the vagina and urine, enzyme-linked immunosorbent assay for perinatal infections (TORCH – infections).

To study the condition of the vaginal microbiocenosis in women of certain groups, a bacterioscopic study of vaginal contents with Gram staining was performed, followed by microscopy with an immersion lens. Bacteriological examination of the contents of the vagina and urine was performed by inoculating the material on nutrient media: 5% blood agar, sugar broth, Endo medium. The crops were incubated at a temperature of 37° C, viewed daily. When growth appeared on dense media, colonies of different morphology were counted, taking into account their ratio. A negative result of the study was found in the absence of growth on all nutrient media for 72 hours. Culture, bacterioscopic and biochemical methods were used to identify microorganisms. Characterization of the vagina biocenosis was performed according to the criteria of E.F. Kira.

Peculiarities of infection in the examined women were investigated by determining the concentration of Ig M and IgG in the blood serum and performed polymerase chain reaction (PCR) for measles virus, cytomegalovirus, parvovirus B19. Serum for the presence of specific immune globulins to these pathogens was examined by ELISA. Enzyme-linked immunosorbent assay systems from Novum diagnostic (Germany) and Strip enzyme-linked immunosorbent assay (Stat fax-300) (USA) were used at a wavelength of 450 nm. Luminescent microscopes ML-2A, LUMAM-II were used to detect specific pathogen antigens by polymerase chain reaction in scrapings of the cervical canal. The method allowed not only detecting the presence of specific hypertension in epithelial cells, but also its typical localization in the structural elements of cells.

Comprehensive ultrasound examination in B-mode was performed to determine the fetometry of the fetus and assess its development with the determination of the estimated mass, location, size and structure of the placenta, the amount of amniotic fluid. To determine the condition of the fetus, a Doppler study of blood flow in the uterine arteries, umbilical artery, middle cerebral artery of the fetus and venous duct (extra placental and fetal hemodynamics) (PHILIPS ATL-HDI 4000, PHILIPS HD 11-XE) was performed. The state of peripheral vascular resistance was assessed by determining the indices - SDR (systolic-diastolic ratio), PI (pulsation index), and IR (resistance index) with the calculation of the cerebra-placental ratio.

Variable-statistical processing of the research results

was performed using the program “Statistica 6.0” with the definition of the main variable indicators: mean values (M), mean errors (m), standard deviations (p). The reliability of the results was determined using the Student’s t test.

## RESULTS AND DISCUSSION

The age, social and marital status of the group of women did not differ significantly. Analyzing the anamnestic data of women in the main group, it was found that 8 (11.1%) patients had births in previous pregnancies with congenital conjunctivitis, 15 (20.8%) – with congenital sepsis, in 39 (54.2%) – with congenital pneumonia, in 1 (1.4%) – with congenital carditis, in 5 (6.9%) – with congenital dacryocystitis and in 4 (5.6%).

Regarding the data of somatic anamnesis, women of the main group had a burdened somatic anamnesis in 58 (80.6%) patients, which was statistically significantly more than in women of the control group – 24 (37.5%) cases. So, in women of the main group, diseases of the urinary system (chronic pyelonephritis, urolithiasis) occurred in 35 (48.6%) cases, respiratory – in 22 (30.6%) cases, from the organs of the gastrointestinal tract – in 15 (20.8%) patients and LOR-organs – in 5 (6.9%) pregnant women. In the control group, chronic pyelonephritis occurred in the anamnesis of 5 (7.8%) pregnant women, urolithiasis – in 4 (6.3%) patients, chronic gastritis occurred in 7 (10.9%) patients and LOR-pathology – in 2 (3.1%). The exacerbation of chronic pathology during pregnancy in women of the main group was observed in 49 (68.1%) cases, while in the control group – in 5 (7.8%). It should be noted that 15 (20.8%) patients of the main group and 7 (10.9%) pregnant women of the control group had manifestations of acute respiratory viral infection during pregnancy of varying severity, which required additional examination and monitoring. In the main group of women, a burdensome obstetric and gynecological history was probably more common: inflammatory diseases of the uterus and appendages were observed in 35 (48.6%) patients, infertility – in 6 (8.3%), functional ovarian cysts and menstrual disorders occurred in 8 (11.1%) and 6 (8.3%) cases, respectively, genital herpes – in 2 (2.8%) women, abortion – in 28 (38.9%), spontaneous abortion – in 6 (8.3%) and frozen pregnancy – in 4 (5.6%) patients. In the control group, inflammatory diseases of the uterus and appendages occurred in 4 (6.2%) cases, abortion – in 8 (12.5%).

Thus, women at high risk of IUI have a burdensome somatic history with exacerbation during pregnancy, which according to the literature is associated with the development of obstetric pathology and the risk of intrauterine infection. In addition, according to the data, women who gave birth to children with IUI were 7 times more likely to have a burdensome obstetric and gynecological history, especially inflammatory diseases, including specific etiology, a history of chlamydia diagnosed in 5 (6.9%) patients, trichomoniasis – in 13 (18.0%), genital mycoplasma – in 4 (5.6%) cases).

Analyzing the course of this pregnancy in women of the

studied groups threatened miscarriage and the threat of premature birth occurred in 24 (33.3%) cases, with signs of isthmic-cervical insufficiency with cervicometry data were diagnosed in 13 (18.1%) patients, which in 1 (1.4%) of the case required the imposition of a cervical suture on the cervix, taking into account the anamnestic data with preliminary preparation and examination. In the control group of patients, the threat of abortion was diagnosed in 15 (23.4%) patients. Examining and managing the women of these groups was carried out according to the order № 417 of the Ukraine Ministry of Health, which requires mandatory microscopic and microbiological examination of vaginal secretions and urine to diagnose bacterial vaginosis and asymptomatic bacteriuria as risk factors for obstetric complications and intrauterine infection. Thus, the normocenosis and the intermediate type of vaginal biocenosis, which is considered a variant of the norm, in women of the main group was found in 15 (20.8%) cases, bacterial vaginosis was diagnosed in 41 (56.9%) cases and nonspecific colpitis in 16 (22.3%) cases. In the control group of patients, bacterial vaginosis was diagnosed in 13 (20.3%) cases and non-specific colpitis in 9 (14.1%), which required appropriate correction according to the diagnosed changes. Regarding the culture of urine, in patients at risk of IUI in 49 (68.1%) cases there was asymptomatic bacteriuria, while hemolytic group B *streptococcus* was diagnosed at a concentration of  $10^5$  or more CFU in 21 (29.2%) pregnant women, which required appropriate treatment during pregnancy and antibiotic prophylaxis of infection during childbirth, in 19 (26.4%) cases diagnosed with group B *streptococcus* and urine at a concentration of less than  $10^5$ , which did not require treatment during pregnancy, but was an indication of mandatory infection prevention in childbirth. Regarding the control group, 12 (18.7%) patients were diagnosed with asymptomatic bacteriuria, and only in 1 (1.6%) case there was group B *streptococcus* in a concentration of less than  $10^5$  (Figure 1).

Separate observation and examination were required for patients with signs of acute respiratory viral disease during pregnancy with various clinical manifestations and severity – 15 (20.8%) patients of the main group and 7 (10.9%) pregnant women in the control group. Thus, fever and general malaise disturbed all women in the groups with acute respiratory viral infection – 22 (31.7%), while intrauterine pneumonia was diagnosed in 9 (12.9%) patients, rash occurred in 5 (7.2%) pregnant women, myalgia – in 4 (5.8%) women. Given the clinical course, these pregnant women were offered a test for cytomegalovirus infection (Figure 2), parvovirus infection and measles examination (Figure 3) (taking into account the epidemic circumstances at the time of the disease).

Therefore, after determining seroconversion in women with clinical symptoms of acute viral infection in 3 (4.3%) cases diagnosed with Ig M and Ig G with low avidity to cytomegalovirus, which may indicate a high risk of fetal infection. When conducting ultrasound examination, one patient was diagnosed with ultrasound markers of infection, namely, hepatosplenomegaly, for which, to clarify the diagno-

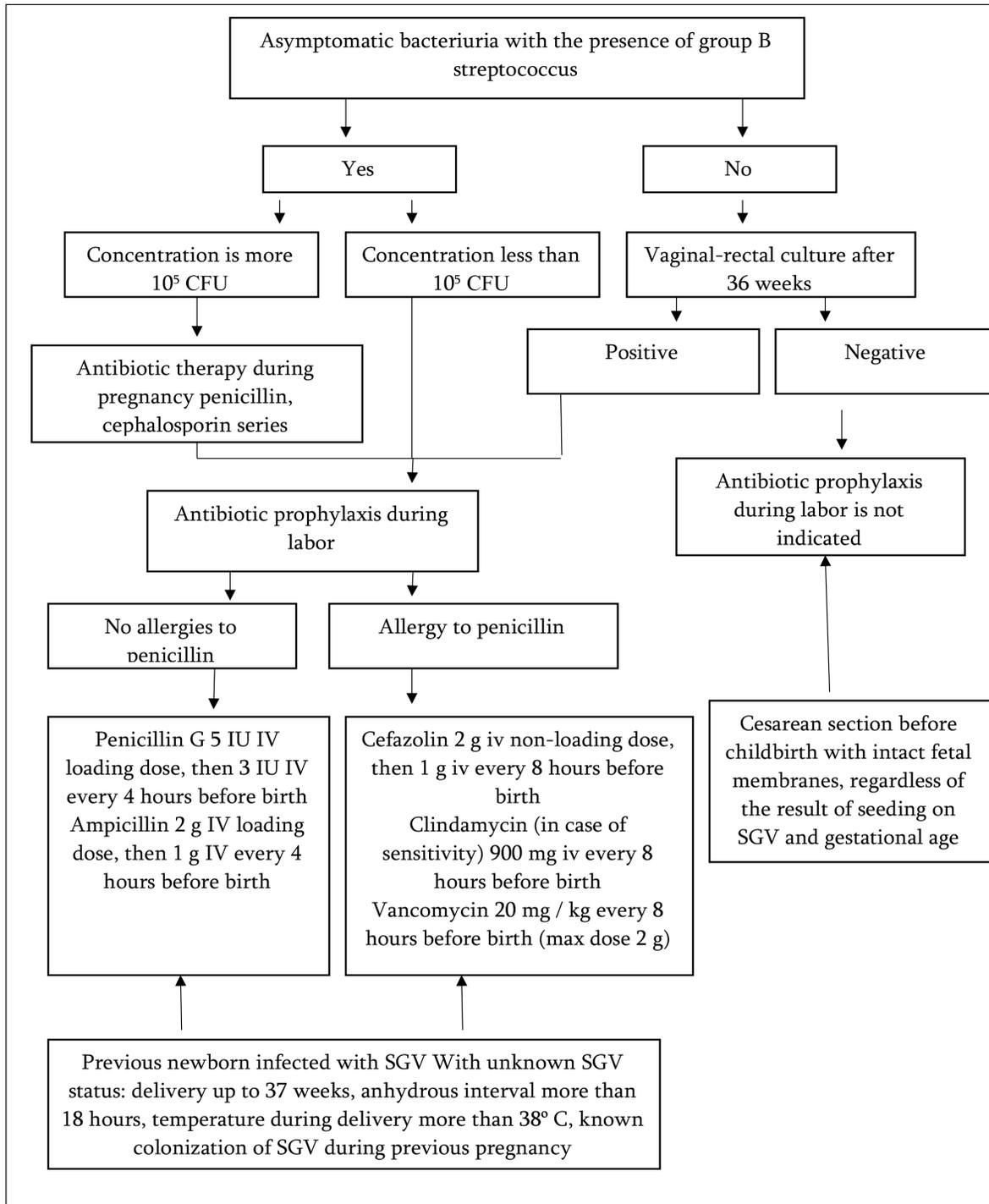
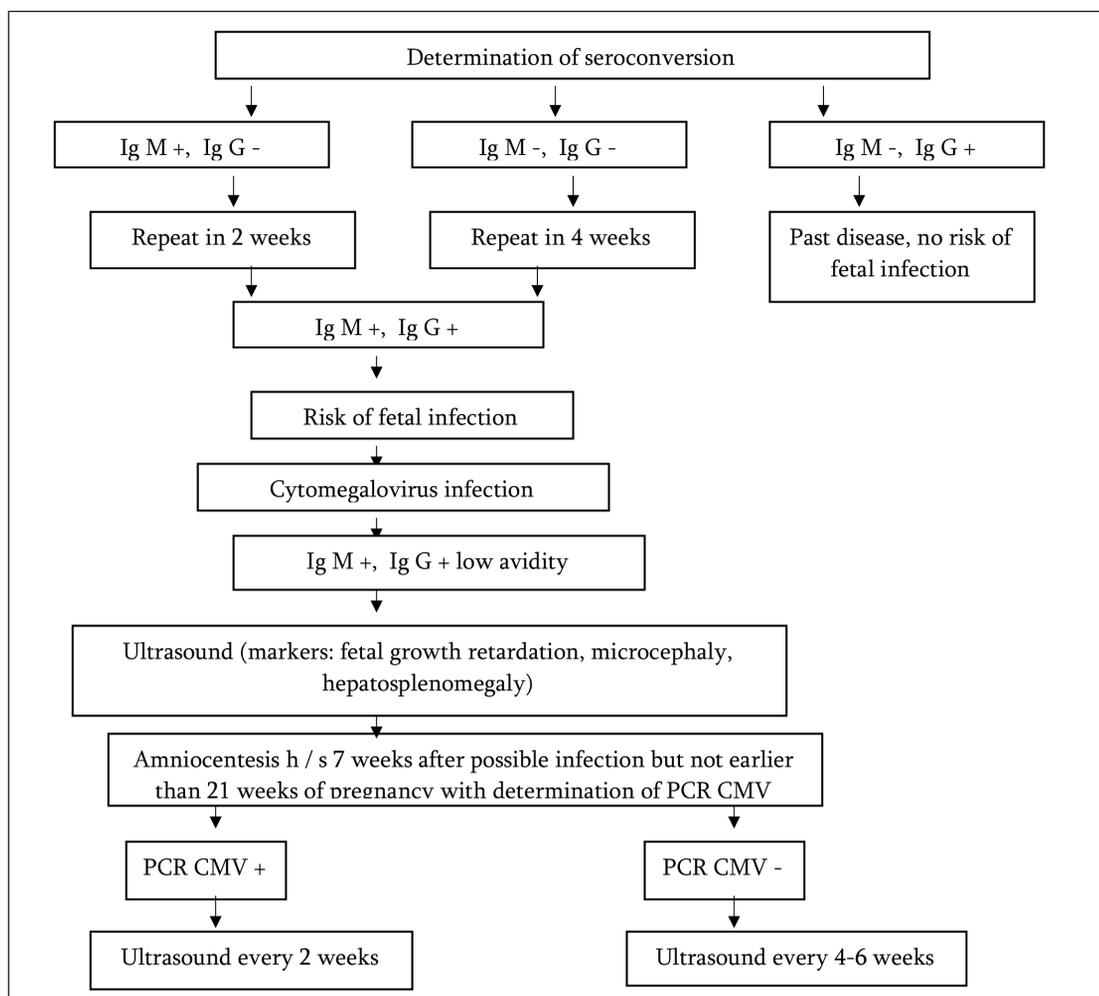


Fig. 1. Algorithm of management of women - carriers of group B streptococcus.

sis and further tactics of managing a pregnant woman, it was proposed to conduct amniocentesis with the determination of cytomegalovirus by the polymerase chain reaction (PCR) method. In 4 (5.8%) patients after the analysis of the epidemic anamnesis examination for measles was performed, taking into account the presence of contact with the patient. In 2 cases, in the absence of Ig G, specific immunoglobulin was administered with repeated Ig G control after 3 weeks.

According to ultrasound examination, patients in the main group in 12 (16.7%) cases were diagnosed with fetal

growth retardation, which required special monitoring during this pregnancy, in 25 (34.7%) patients at high risk of IUI there were changes in the placenta, namely, hyper echogenic inclusions in the placenta occurred in 7 (9.7%) cases, dilation of the intervillous space in 8 (11.1%) cases, placental hyperplasia in 7 (9.7%) cases, polyhydramnios was diagnosed in only 5 (6) , 9%) cases, with 1 (1.4%) acute polyhydramnios in patients with signs of SARS during pregnancy. At the same time, ultrasound changes in placenta and water volume did



**Fig. 2.** Algorithm for managing women with CMV infection.

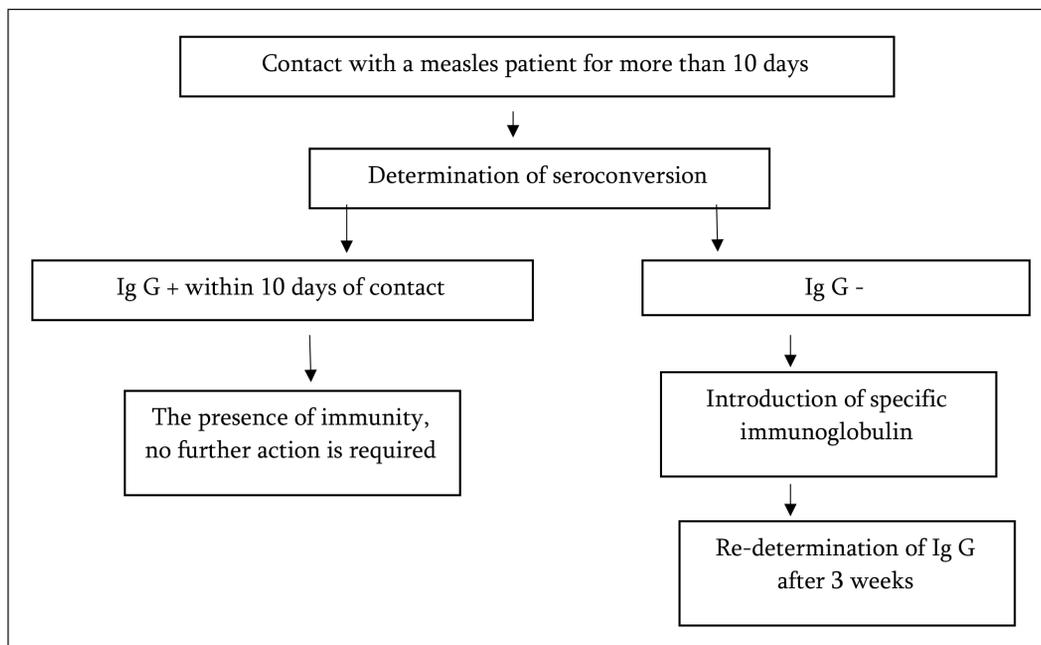
not have a statistically significant difference in women in the control group, except for the percentage of cases with fetal growth retardation, which were not in women at low risk of IUI.

Investigating the hemodynamic characteristics of the uterine-placental-fetal complex, an increase in the resistance index in the uterine arteries in women of the main group from  $0.53 \pm 0.03$  to  $0.68 \pm 0.06$ , in the control – from  $0.48 \pm 0.02$  to  $0.95 \pm 0.19$  due to the slowing of diastolic blood flow, also applied to the pulsation index –  $0.97 \pm 0.02$  in women at increased risk of IUI. Hemodynamics in the umbilical artery in women of the main group was characterized by an increase in IR of  $0.71 \pm 0.02$ , in the control – from  $0.61 \pm 0.01$ , PI –  $0.97 \pm 0.03$  and  $0.89 \pm 0.05$ , respectively, indicating a violation of placental and fetal blood flow at high risk of IUI. Thus, dopplerometry in women of the main group revealed a violation of uteroplacental blood flow in 4 (5.6%) cases, fetal-placental – in 16 (22.2%) and uteroplacental-fetal blood flow – in 5 (6.9%) cases, in women of the control group there was a violation of uteroplacental blood flow in 2 (3.1%) cases.

Regarding the course of childbirth, in 53 (73.6%) cases in women of the main group childbirth was urgent, premature birth took place in 19 (26.4%) cases, with only 5 (6.9%) patients there was a need premature birth due to anenatal fetal

distress and in 14 (19.5%) there was a premature rupture of membranes (PRPO). In the control group of women, premature births occurred in 8 (12.5%) cases, in 4 (6.2%) on the background of PRPO. The course of preterm labor in women of both groups was statistically significantly different. Thus, in women with high risk of IUI there was PRPO in 6 (8.3%) cases and in the control group – in 4 (6.2%), weakness of labor developed in 10 (13.9%) patients of the main group and in 8 (12.5%) in the control. 15 (20.8%) women in the main group gave birth by cesarean section, of which 4 (5.5%) from fetal growth retardation and 11 (17.2%) from the control group.

The average weight of newborns in women at high risk of IUI was –  $3344.0 \pm 101.0$ , height  $51 \pm 4$  cm, in the control  $3540.2 \pm 119.1$ , height  $52 \pm 3$  cm. The Apgar score of the newborns of the main group at the first minute was  $7.8 \pm 0.5$  points, at the fifth minute –  $8.3 \pm 0.5$  points and there was no significant difference with the newborns of the control group ( $7.9 \pm 0.5$  and  $8.6 \pm 0.4$ , respectively). Most newborns did not need primary resuscitation in the delivery room. In women of the main group, 4 (5.5%) children were born in severe asphyxia; they were born prematurely due to Antenatal distress against the background of fetal growth retardation; in a state of moderate asphyxia, 5 (6.9%) children were born with mild asphyxia – 5 (6.9%).



**Fig. 3.** Algorithm for managing women with suspected measles.

Regarding children in the control group, the average and mild degree of asphyxia at birth occurred in 3 (4.8%) and 4 (6.2%) cases, respectively, which was statistically significantly different. In children with severe asphyxia, neurological symptoms occurred in the form of moderate depression of the central nervous system, increased neuro reflex excitability. In 3 (4.2%) children of the main group there was a cephalohematoma, which may be associated with IUI, in 4 (5.6%) hemorrhagic syndrome in the form of skin and hemorrhagic manifestations, toxic erythema with small papular rash on the trunk and extremities, which disappeared on its own 4-7 days after birth.

## CONCLUSIONS

1. Thus, as a result of the study, risk factors for intrauterine infection were identified, namely, burdened obstetric and gynecological history (artificial abortions – 48.6%, inflammatory diseases of the uterus and appendages – 38.9%), burdened somatic history – 80.6% (diseases of the urinary system – 48.6%, respiratory system – 30.6%, gastrointestinal tract – 20.8%, manifestations of acute respiratory viral infection during pregnancy – 31.7%, which requires additional examination for a specific infectious process with appropriate monitoring of this pregnancy).
2. Women at high risk for IUI require close monitoring of the fetus due to the increased frequency of hemodynamic changes in uteroplacental-fetal circulation, including fetal-placental – 22.2% and the occurrence of intrauterine growth retardation.
3. Carriers of group B *streptococcus* – 55.6% is an important risk factor for IUI and requires mandatory treatment during pregnancy at urinary concentrations of more than  $10^5$  CFU with subsequent antibiotic prophylaxis in

childbirth, women with no culture of *streptococcus* B in the urine need screening for its carrier by vaginal-rectal culture at 36 weeks of pregnancy.

4. Women with an undetermined status regarding group B *streptococcus* in case of delivery earlier than 37 weeks, with an anhydrous interval of more than 18 hours, an increase in body temperature during childbirth above  $38^{\circ}$  C, at birth of a child infected with group B *streptococcus* during previous vaginas, need mandatory antibiotic prophylaxis during childbirth.
5. Women with suspected cytomegalovirus infection require determination of seroconversion; in case of immunologically confirmed infection, it is desirable to recognize PCR for cytomegalovirus in the amniotic fluid in order to determine further management and monitoring of this pregnancy.

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#### Conflict of interest:

*The Authors declare no conflict of interest.*

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**A** – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis,

**D** – Writing the article, **E** – Critical review, **F** – Final approval of the article